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09/463,890	04/28/2000	ULRICH H. KOSZINOWSKI	203676	6925

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/463,890	KOSZINOWSKI ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,37 and 40-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 37, 40-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 21 June 2007 in response to the Final Office Action mailed 21 March 2007. Finality of the 21 March Office Action is **withdrawn** in view of the new grounds for rejection set forth herein below.

Claims 36, 37, 40-70, 73 and 74 were considered in the 21 March Office Action. Claims 73 and 74 were cancelled in the 21 June Paper. Claims 36, 37, 40-70 are pending and under consideration.

Claim Rejections - 35 USC § 101

Claims 51-56 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed to a cell comprising the claimed BAC. The specification at page 8 contemplates using the disclosed vectors as drugs, preferably for performing somatic gene therapy, or as a vaccine, which would involve introducing the vectors into human cells *in vivo*. Given these teachings, the broadest reasonable interpretation of the claim clearly encompasses a cell that might be present or is intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

Amending the claims to recite "An isolated host cell…" would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36, 37, 40, 42, 48, 51, 54, 57, 58, and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Messerle et al. (1996) *J. Mol. Med.* 74:B8 (previously made of record).

The claims were previously indicated allowable over the teachings of Messerle et al. because the limitation "an infectious herpes virus genomic sequence" was construed as requiring that the herpes virus genomic sequence comprised by the BAC have the capacity to generate an infectious herpes virus in the absence of any helper functions provided by nucleic acids outside of the BAC. However, upon further consideration of the claim limitations in view of the teachings of the specification, it is concluded that this is not the broadest reasonable reading of the claims.

The specification teaches, "The expression 'infectious viral genome sequences' within the meaning of the invention covers both the complete genome and those parts of the genome of a virus that are indispensable for replication and packaging in a host organism or host cell." Thus, the definition of infectious genome sequences appears to extend to any part of the genome of a virus that is necessary for replication and packaging in a host organism without requiring that the sequences comprised by the virus as a whole are sufficient for replication and packaging. Thus, the claims cover a BAC comprising any gene necessary for replication and packaging in a

host organism or host cell, so long as the genomic sequence comprised by the BAC is larger than 100kb or, in the case of claim 37, 200kb.

Messerle et al teach the construction of two BAC/MCMV hybrids wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further teaches that the constructs were used to produce MCMV virions (i.e., due to complementation between the two vectors upon co-transformation in eukaryotic host cells). The ability of the BAC vectors to produce infectious virus evidences that each of the vectors comprise "parts of the genome of a virus that are indispensable for replication and packaging". Therefore, the BACs of Messerle et al. anticipate the BAC of the instant claims 36, 37, 40 and 42 and the host cell of claims 51 and 54. Furthermore, Messerle et al. teaches production of the BAC vectors by cotransfection in *E. coli* cells, which method anticipates the method of claims 57, 58 and 64-66.

The vector, host cell and method of Messerle et al. comprises all of the limitations of the instant claims. Therefore, the claims are anticipated by Messerle et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*).

The claim is directed to the BAC of claim 40, wherein the herpes virus is a human cytomegalovirus. As described above, Messerle et al. teaches a BAC vector according to the limitations of claim 40 but does not explicitly teach a BAC vector comprising infectious genomic sequence of a human CMV. However, Messerle et al. teaches that the purpose of constructing the BAC vectors was to facilitate the exchange of nonessential viral genes by any gene of choice without the need for further selection. Furthermore, Messerle et al. notes that human CMV as well as mouse CMV comprises a region that is probably not essential for replication *in vitro* and clearly views human CMV as a potential vector. In view of these teachings, one of skill in the art would be motivated to make a BAC vector from human CMV as demonstrated for mouse CMV in order to facilitate the exchange of nonessential viral genes by any gene of choice without the need for further selection. Absent evidence to the contrary, one would have a reasonable expectation of success in obtaining a BAC vector comprising infectious genomic sequence of a human CMV because Messerle et al. demonstrates the production of a BAC with the similar mouse CMV.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tomkinson et al. (1993) *J. Virol.* 67:7298-7306 in view of Messerle (*supra*).

Tomkinson et al. teaches the reconstitution of infectious Epstein-Barr virus by cotransfection of five overlapping cosmid clones comprising the entire EBV genome. (See especially Figure 1 and the caption thereto, the paragraph bridging the left and right columns on page 7299, and the section entitled "Type 1 EBV recombinants following transformation of five overlapping EBV DNA fragments into cells containing a defective type 2 EBV" beginning on page 7300). Tomkinson further teaches that the purpose of the experiments described therein is to provide a general strategy for constructing EBV recombinants which are specifically mutated at any site in the EBV genome. Tomkinson does not teach construction of a BAC comprising an infectious EBV genomic sequence.

As described above, Messerle et al teach the construction of two BACs comprising herpes virus genomic sequences wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb, and further teaches that the constructs were used to produce virions due to complementation between the two vectors upon co-transformation in eukaryotic host cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made do modify the EBV constructs of Tomkinson et al. according to the teachings of

Messerle et all. to produce BAC vectors comprising portions of the EBV genome of greater than 100 kb (the EBV genome is approximately 170 kb). One would be motivated to combine the teachings in view of the fact that Messerle et al. demonstrates that infectious herpes virus could be produced by cotransfection of only two BAC vectors, as opposed to the five cosmid vectors required by the method of Tomkinson et al. Therefore, use of BAC vectors would save time and expense in the production of vectors for cotransfection as well as improve the efficiency with which recombinants are produced by requiring only a single recombination event, as opposed to the multiple recombination events required to obtain infectious virus using five cosmid vectors.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings of the prior art in view of the fact that Messerle et al. demonstrates the efficacy of BAC vectors as vehicles for cloning large herpes virus genomic DNA such that recombinants can be obtained by cotransfection.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tomkinson et al. (*supra*) in view of Messerle et al. (*supra*), as applied to claim 43 herein above, and further in view of Ehtisham et al. (1993) *J. Virol.* 67:5247-5252.

As described above, the invention of claim 43 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Tomkinson et al. and Messerle et al. Tomkinson et al. and Messerle et al. do not teach a BAC

containing a murine gamma herpes virus 68. However, Tomkinson et al. teaches that the method described therein has utility for constructing EBV recombinants specifically mutated at any site in the EBV genome for the purpose of studying the virus. (See especially the paragraph bridging the left and right columns on page 7298, the first full paragraph on page 7304 and the first full paragraph in the right column on page 7304.)

Ehtisham et al. teaches that the murine herpes virus 68 (MHV-68) is a naturally occurring murid herpes virus closely related to the EBV of primates. (See especially the first paragraph after the abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a BAC according to the teachings of Tomkinson et al. and Messerle et al. comprising an infectious herpes virus genomic sequence of MHV-68 as taught by Ehtisham et al. As described above, Tomkinson et al. teaches that the method described therein has utility for constructing EBV recombinants specifically mutated at any site in the EBV genome for the purpose of studying the virus and Ehtisham et al. teaches that MHV-68 is a murine herpes virus related to EBV that is of interest. Therefore, the skilled artisan would be motivated to combine the teachings of the prior art in order to study the effects of targeted mutations in the MHV-68 genome as well.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings of the prior art in view of the fact that Messerle et al. demonstrates the efficacy of BAC vectors as vehicles for cloning large herpes virus genomic DNA such that recombinants can be obtained by cotransfection.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 45-47, 49, 50, 52, 53, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*), as applied to claim 36 herein above, in view of Gage et al. (1992) *J. Virol.* 66:5509-5515.

The claims are directed to a BAC comprising an infectious herpes virus genomic sequence larger than 100kb, wherein the bacterial nucleic acid sequences are flaked by loxP sites. As described above, Messerle et al. teaches a BAC vector according to the limitations of claim 36 wherein the BAC is produced by homologous recombination in a bacterial cell. Messerle et al. does not teach that the bacterial nucleic acid sequences are flaked by loxP sites.

Gage et al. teaches a method of inserting plasmid DNA into a herpes virus genome by Cre-lox recombination wherein the bacterial sequences are flanked by loxP sites (see especially the paragraph bridging pages 5509-5510, Figure 1 and the caption thereto) and teaches that the method has many advantages over methods of inserting bacterial DNA by homologous recombination using marker transfer (see especially the first full paragraph on page 5514).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of producing a BAC comprising an infectious herpes virus genomic sequence according to the method of Gage et al. such that the product BAC comprises bacterial nucleic acid sequences flanked by loxP sites. One would be motivated to use the method of Gage et al. in view of the many advantages of the method described in the teachings

of Gage et al. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings of the prior art because Gage et al. demonstrates the efficacy of the Cre-lox system for inserting bacterial DNA into the herpes virus genome.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*) in view of Roizman et al. (1985) *Science* 229:1208-1214.

The claims are directed to a method of producing the BAC of claim 36 comprising introducing bacterial nucleic acid sequences into a host cell containing infectious herpes virus genomic sequences and (b) recombining the bacterial nucleic acid sequences with the infectious herpes virus sequences, wherein the host cell is a eukaryotic cell.

As described above, Messerle et al. teaches a method of producing the BAC of claim 36 by homologous recombination in bacterial cells. Messerle et al. does not teach the method practiced in a eukaryotic cell.

Roizman et al. teaches that it was well known in the art at the time the invention was made that bacterial sequences could be inserted into the genome of herpes virus by a method of recombination in eukaryotic cells which could be practiced efficiently using TK selection. (See especially Figure 2 and the caption thereto and the section entitled "*Construction of novel genomes*" beginning on page 1211.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of producing a BAC comprising an infectious herpes virus genomic sequence according to the method of Roizman et al. One would be motivated to use any method that provides efficient insertion of bacterial DNA into the HSV genome when practicing the method of Messerle et al. and Roizman et al. teaches that the method described therein provides for efficient insertion of heterologous sequences into herpes virus genomes.

One would have a reasonable expectation of success in combining the teachings of the prior art because Roizman et al. demonstrates the efficacy of the eukaryotic cell homologous recombination system for inserting bacterial DNA into the herpes virus genome.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*) in view of Roizman et al. (*supra*) and further in view of Chen et al. (1987) *Mol. Cell. Biol.* 7:2745-2752.

The claims are directed to a method of producing the BAC of claim 36 comprising introducing bacterial nucleic acid sequences into a host cell containing infectious herpes virus genomic sequences and (b) recombining the bacterial nucleic acid sequences with the infectious herpes virus sequences, wherein the host cell is an NIH3T3 cell and the bacterial nucleic acid sequences are introduced by calcium phosphate precipitation.

As described above, the teachings of Messerle et al. and Roizman et al. render obvious the method practiced in eukaryotic cells. Messerle et al. in view of Roizman et al. does not teach a specific cell type or method of transfection.

Chen et al. teaches a method of efficiently transfecting eukaryotic cells, including NIH3T3 cells, by a method involving calcium phosphate coprecipitation. (See especially the abstract and Table 1.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Messerle et al. in view of Roizman et al. by any method established to provide efficient transfection. One would be motivated to practice the method by calcium phosphate transformation of NIH3T3 cells because Chen et al. teaches that the method provides efficient transformation. One would have a reasonable expectation of success in combining the teachings of the prior art because Roizman et al. demonstrates the efficacy of the eukaryotic cell homologous recombination system for inserting bacterial DNA into the herpes virus genome and Chen et al. teaches an efficient method for introducing DNA into eukaryotic cells.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (*supra*) in view of Luckow et al. (1993) *J. Virol.* 67:4566-4579 (previously made of record).

The claims are directed to a method of mutagenizing the infectious herpes virus genomic sequence of claim 36 comprising introducing the BAC of claim 36 into a bacterial host and

exposing the BAC to mutagenizing DAN molecules, wherein there is a transposon in the mutagenizing DNA molecules.

As described above, Messerle et al. teaches the construction of a BAC having all of the properties of the BAC of the instant claim 36. Furthermore, Messerle et al. teaches that the BACs will facilitate the exchange of nonessential viral genes by any gene of choice. Messerle does not specify how the exchange of genes should be carried out.

Luckow et al. teach the construction and use of BAC vectors (i.e. baculoviral shuttle vectors) that comprise an infectious viral genome sequence operatively fused to a mini-F replicon that allows autonomous replication and stable segregation of plasmids at low copy number in *E. coli*. The BAC vectors further comprise a selectable kanamycin resistance marker and attTn7 sites that allow transposon-mediated insertion of heterologous nucleic acid sequences into the vector (e.g. Abstract; page 4567, columns 1-2, bridging paragraph; Figure 1). Luckow et al further teach transposon-mediated mutagenesis at the attTn7 sites of different BAC vectors in *E. coli* to generate new vectors comprising a heterologous sequence encoding a desired polypeptide. (See especially the section entitled "Transposition of mini-Tn7 elements to target bacmids" bridging the left and right columns on page 4573.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the transposon mediated DNA exchange described by Luckow et al. for the purpose of exchanging nonessential viral genes with gene of choice in the BACs of Messerle et al. One would be motivated to combine the teachings of the prior art because Messerle et al. teaches that intended use of the BAC vectors described therein is to facilitate the exchange of nonessential CMV viral genes by any gene of choice and Luckow et al. teaches that the method

of the transposon mediated DNA exchange described thereby provides many advantages over other methods of engineering viral genomic DNA comprised in BACs that were known in the prior art. (See especially the first full paragraph on page 4577.)

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings of the prior art because Luckow et al. demonstrates the efficacy of transposon mediated DNA exchange as a means to insert heterologous DNA into a BAC comprising an infectious viral genomic sequence.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner
Art Unit 1636